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Research report

Striatal dopamine D_1 receptors in type 1 and 2 alcoholics measured with human whole hemisphere autoradiography

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Abstract

A considerable number of human and animal studies have implied the importance of dopamine system and alterations in dopamine receptors in the context of alcoholism. However, it has remained unclear if the alcohol-abuse related dopaminergic deficit is specifically associated with certain receptor subtype. The aim of this study was to compare putative alterations of dopamine D_1 receptors in caudate and putamen of nine type 1 alcoholics, eight type 2 alcoholics and 10 healthy controls by using [^{3}H]SCH 23390 as a radioligand in postmortem human whole hemisphere autoradiography. In addition, we compared the present results to our earlier studies on dopamine transporters and dopamine D_2 receptors in these same subjects and evaluated the putative correlations of dopamine D_1 receptor densities between the nucleus accumbens and the abovementioned structures. Our results show that alcoholics do not have significantly different striatal dopamine D_1 receptor densities compared to controls. Neither were there any significant correlations between the dopamine D_1 receptors and the two other dopamine binding sites. However, the correlations of the dopamine D_1 receptors between nucleus accumbens and dorsal striatal structures were consistently and mostly statistically significantly positive in alcoholics, but not in controls, which may suggest some pathology related to addiction. In addition, considering the facts that dopamine D_1 receptors were more abundant in the mesolimbic nucleus accumbens than in the caudate or putamen and that there was a strong tendency towards lower binding among type 1 alcoholics may suggest the importance of dopamine D_1 receptors in reward and/or alcoholism.

Theme: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: Alcoholism; Autoradiography; Dopamine; Receptor; Human brain; Striatum

1. Introduction

Ethanol acutely increases brain dopamine (DA) activity and microdialysis studies have shown an induction of DA release in the caudate and nucleus accumbens (NAC) after acute ethanol intake [15]. The effects of DA are regulated by a family of G protein-coupled DA receptor subtypes, which include D_1–D_5 receptor subtypes [31] and animal models of alcoholism have implied involvement of DA D_1 receptors in ethanol self-administration with animals specially bred or trained for ethanol preference [35,42,43,61]. In addition, human studies on other drugs that also induce an increase in extracellular DA [39] have suggested an involvement of DA D_1 receptor in the context of addiction: DA D_1 receptor protein has been reported to be increased in human chronic methamphetamine users [71] and long-acting DA D_1 antagonist, ecopipam, has been shown to enhance smoked

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cocaine self-administration [27]. Although there are several studies reporting lower striatal DA transporters (DAT) and DA D_2 receptors among alcoholics, there are no studies on striatal DA D_1 receptors in these patients.

Late onset type 1 alcoholics with the empathic, compassionate and socially dependent character traits have been suggested to have an underlying dopaminergic deficit, as opposed to the serotonergic deficit observed in teenage onset type 2 alcoholism, which is characterized by vengeful and socially hostile character [11]. SCH 23390 is perhaps the most widely used ligand to study DA D_1-like (D_1 and D_5) receptors both in vitro and in vivo [17,22,23,37,60,62]. It also binds to 5-HT_2 receptors [23], which in this study was blocked by the addition of ketanserin. Whole hemisphere autoradiography provides high resolution images corresponding to in vivo (i.e., PET and SPET) studies, and enables more detailed study of various brain structures.

In the present study we tested several hypotheses. First, we studied whether the DA D_1 receptor densities in the dorsal striatum (caudate, putamen) differ between the alcoholic subgroups and controls. Second, we compared in the same subjects the densities of DAT [65,67], which can be used as a marker of neuronal density in these regions [8] to densities of mostly postsynaptic DA D_1 receptors. Third, because animal studies have implied that some intermediate DA D_1 activation is required to observe DA D_2 effect to ethanol self-administration [35], we compared the present results also to our earlier studies on DA D_2 receptors in these same subjects [67]. Fourth, we have previously shown striatal DAT and DA D_2 receptor binding to correlate between the mesolimbic NAC and dorsal striatum and a similar striatum vs. extrastriatum correlation has been shown in one SPET study in type 1 alcoholics, but not in controls [54,65,67]. Therefore we evaluated also the correlations of [^{3}H]SCH 23390 binding between the NAC [68] and dorsal striatum to test whether relative individual densities of these receptors are maintained in different brain areas in these three groups.

2. Materials and methods

The procedure has been described in detail previously [23,68].

2.1. Brain sampling

Human brain left hemispheres used were obtained during clinical necropsy at the Department of Forensic Medicine, University of Oulu, Finland, and the Department of Forensic Medicine, University of Kuopio, Finland. The Ethics Committee of the University of Oulu and the National Institute of Medicolegal Affairs, Helsinki, Finland, approved the study. Medical records on the cause of death, previous diseases and medical treatments of controls and alcoholics were collected.

2.2. Diagnostics

Two physicians, independently of each other made diagnoses. Mental disorders were coded according to Diagnostic and Statistical Manual of Mental Disorders, third edition-revised diagnostic criteria [2] and alcoholics were subclassified as type 1 or 2 according to Cloninger [11]. Kappa coefficient of diagnostic agreement [12] was 0.9; i.e., one type 2 alcoholic included in the study was diagnosed as a type 1 alcoholic by the second diagnostician. Otherwise diagnoses were unanimous. Subjects having any diseases (such as epilepsy or psychotic disorders), or taking medication that affect the central nervous system (such as antipsychotics or antidepressants), were excluded.

2.3. Study subjects

All 27 cases were Caucasians. The study groups consisted of nine type-1 alcoholics (seven males, two females; mean age 52.7 years; postmortem delay 11.9±4.5 h; mean±S.D.), eight type 2 alcoholics (males; mean age 34.6 years; post mortem delay 14.1±3.4 h; mean±S.D.) and 10 controls (eight males, two females; mean age 53.5 years; postmortem delay 14.8±9.2 h; mean±S.D.) free of psychiatric diagnosis. Postmortem delays between the groups were not significantly different (P=0.62–0.98, Scheffe's test for multiple comparisons, two-tailed). Alcoholism among these subjects was severe judging by the frequent admissions to emergency stations and doctors appointments due to alcohol related problems and the diagnosis of alcoholism itself was not a difficult task even without interviews. Eight of the nine type 1 alcoholics had alcohol in their blood at their time of death, and one alcoholic (included in all ligand binding studies) had had an abstinence period of 10 h. One of the controls had a small amount of alcohol in his blood at the time of death (0.036%). Two of the type 1 alcoholics had traces of diazepam in their blood samples. Six type 2 alcoholics had alcohol in their blood at the time of death, three had traces of benzodiazepines and one was positive for cannabinoids. One had an abstinence period of 5 days and one of three to 7 days. Mean alcohol concentration in the blood was 0.20±0.17% (mean±S.D.) in the type 1 alcoholic group and 0.19±0.14% in the type 2 alcoholic group and the two groups did not differ in this respect [F(0.174), P=0.90, independent samples t-test]. All subjects died of sudden causes. Nine controls died because of myocardial infarction and one of aorta rupture due to dissecting aortic aneurysm. The causes of death in the type 1 alcoholic group were pneumonia (2), lethal ethanol intoxication (2), myocardial infarction (2), suicide by hanging (1), pancreatitis (1) and subdural haematoma on the right side (1). The causes of death in the type 2 alcoholic group were suicide by hanging (3), knife wound (2), gunshot wound (1), rupture of heart due to a car accident (1) and cardiac death (1). Evaluation of the duration of heavy alcohol use or smoking based only on